IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/009,473	Group Art No.:	1648
Filed:	November 8, 2001	Examiner:	Emily M. Le
Applicant:	Michael Hagen		
Confirmation No.:	3152		
Customer Number:	25291		
Docket Number:	ACY33482		
Title:	ADJUVANT COMBINATION FORMULATIONS		

Mail Stop AF
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

March 4, 2009

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

In the above-referenced application, a Final Office Action dated March 19, 2008, rejected claims 88-90,98,105,109,116-119,160,163,164 and 167 under 35 U.S.C. § 103(a) as allegedly being obvious over cited prior art. A Final Office Action dated December 4, 2008 maintained the rejection of these claims in view of the same cited prior art. The basis for maintaining the rejection was the same as that provided in the Office Action dated March 19, 2008. As such, the claims in the present application have been twice rejected and qualify for appeal. Accordingly, the following remarks are being submitted together with a Notice of Appeal under 37 C.F.R.§ 41.31 in support of a Pre-Appeal Brief Request for Review.

Applicant believes that the outstanding rejection of record is improper and without basis. In support of this position, Applicant presents the following legal and/or factual deficiencies in the rejection.

Pending Claims

The pending claims are drawn to a composition consisting of an antigen with 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A in combination with granulocyte macrophage colony stimulating factor (GM-CSF), together with a diluent or carrier that can be used in the form of a stable oil-in water emulsion. This adjuvant-cytokine formulation is used to enhance the immune response in a vertebrate host to an antigen, wherein the antigen is derived from a pathogenic virus, particularly polypeptides, peptides or fragments derived from the human immunodeficiency virus (HIV).

Additionally, methods are claimed to elicit an immune response by administering said composition to a host wherein the immune response elicits cytotoxic T- lymphocytes (CTL).

The invention described herein discloses that the combination of an antigen, a selected cytokine, and an immunostimulating complex lipid adjuvant, MPL, increases the immune response specific for the antigen. The invention is exemplified in a model system using peptide antigens derived from HIV. The claimed antigen-cytokine-adjuvant combination induces high titers of antigen-specific and virus neutralizing antibody and also induces good cellular responses as determined through induction of CTL.

Rejection on Appeal

Claims 88-90 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich et al. (Vaccine Design. Plenum Press, New York, N.Y., pg. 495-523, hereafter "Ulrich") and Disis et al. (Blood, 1996; Vol.88, No.1:202-210,hereafter "Disis"). The Examiner contends that Ulrich taught that the immunostimulant MPL delivered in aqueous admixtures, in oil and water emulsions,

or in liposomal vehicles, has adjuvant activity. The Examiner also asserts that Disis taught that GM-CSF is an effective adjuvant. It is the Examiner's opinion that both Ulrich and Disis teach adjuvant compositions that would allegedly be prima facie obvious to combine to yield Applicant's claimed invention.

Claims 88, 98 and 116-119 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis as applied to claim 88, in view of Bartlett et al. (hereafter "Bartlett). Bartlett is cited for teaching the same amino acid sequence as SEQ ID NO:2 of the present invention to elicit an HIV-antigen specific response. The Examiner contends that it would have been prima facie obvious for one skilled in the art at the time the invention was made to combine the adjuvant composition of Ulrich and Disis with the HIV antigen of Bartlett.

Claims 88, 98, 105, 109, 116, 160, 163-164 and 167 stand rejected under 35 USC §103(a) as allegedly being obvious over Ulrich and Disis in view of Bartlett, as applied to claims 88, 98 and 116. The Examiner asserts the opinion that in addition to the previous rejections regarding Applicant's claimed composition that the administration of the antigen in Bartlett would necessarily induce a CTL response in the subject because the antigen of Bartlett contains CTL specific epitopes and would necessarily induce a CTL response.

Basis for Request for Pre-Appeal Review

Based on the cited references, the Examiner asserts that it would have been obvious to one skilled in the art to combine the cited individual prior art elements cited to yield Applicant's claimed invention. Applicant respectfully submits that the Examiner has failed to articulate *why* it would have been motivating to one of ordinary skill in the art to combine the prior art elements to yield Applicant's claimed invention. The Examiner has also failed to establish a prima facie case of obviousness by failing to meet the standard of the KSR decision (KSR International Corporation v. Teleflex In. (KSR), 550 U.S. __, 83 USPQ2d 1395 (2007)) by failing to articulate why someone skilled in the art would have *predicted* the utility of the combination of elements in Applicant's claimed invention. The Examiner has also failed to apply the PTO guidelines regarding the KSR decision.

With respect to the stated §103 (a) rejection, a key aspect to the rejection is the Examiner's continued assertion that MPL and GM-CSF are "art-recognized equivalents", as stated throughout the office actions dated March 19, 2008 and December 4, 2008. The Examiner contends that because MPL and GM-CSF are both allegedly "adjuvants", it would have been obvious to one of ordinary skill in the art to combine them into one composition to enhance the immune response against an antigen of interest. The Examiner has rejected all of the pending claims in view of Ulrich and Disis and in further view of Bartlett.

Ulrich discloses that the immunostimulant complex lipid MPL delivered in aqueous admixtures, in oil-in-water emulsions, or in liposomal vehicles, has adjuvant activity. Nowhere in this reference do the authors teach or suggest the combination of antigen and MPL and a cytokine, specifically GM-CSF. Disis discloses GM-CSF to be an effective immunomodulator, but without any teaching or suggestion to combine GM-CSF with any other adjuvant or cytokine.

The Applicant submits that there is nothing in Ulrich or Disis that would prompt the skilled artisan to combine an antigen with the claimed combination of MPL and a cytokine, specifically GM-CSF. The Examiner does not point to specific information in Disis that suggests its combination with Ulrich to yield the claimed invention. Instead, the Examiner has cited a passing reference to the combination of MPL and TDM on page 510 of Ulrich. Applicant has argued that the claimed invention of the present application is directed to the combination of an adjuvant and a cytokine. TDM is not a cytokine. TDM is a general activator that causes a severe reaction in subjects upon administration. TDM is vastly different than a cytokine and should not be equated as such. There is no teaching or suggestion in Ulrich to combine MPL with a cytokine or lymphokine, and more specifically GM-CSF. GM-CSF activates the immune system in a very specific manner using pathways within the immune system vastly different that the general inflammatory response generated by TDM. Besides, as stated below, there is no way of predicting a synergistic reaction between MPL and GM-CSF merely by reading that combining MPL and TDM enhance an immune response.

The individual references cited by the Examiner establish the properties of the individual elements without any teaching or suggestion to combine these elements. There is nothing in the cited references to suggest to the skilled artisan - ***nor*** to the Examiner having Applicant's specification in hand with legally impermissible hindsight - that the combination of MPL plus GM-CSF would have been obvious at the time the claimed invention was made.

In lieu of an explanation as to ***why*** one of skill in the art would be motivated to combine the references, the Examiner instead cited *In re Kerkhoven* and MPEP §2144.06 in support of this rejection. In both referenced Office Actions the Examiner asserted that "it is the position of the Examiner, that since both MPL and GM-CSF function as adjuvants, therefore they are art-recognized equivalents". The Examiner also asserted the combination of references provide scientific evidence as to why the skilled artisan would combine the teachings of these references to arrive at the claimed invention. Applicant continues to traverse this rejection.

In relying on *In re Kerkhoven*, the Examiner concluded that the Applicant's invention is the combination of two compositions that are art-recognized equivalents. Applicant maintains that an adjuvant and a cytokine are ***not*** art-recognized equivalents. Arguments and exhibits presented on pages 17-18 of Applicant's response of September 19, 2008 define the art-recognized differences between an adjuvant and a cytokine. Furthermore, supporting arguments were submitted in the form of a Declaration from Michael Hagen, Ph.D, under 37 CFR §1.132 which accompanied Applicant's response dated September 17, 2008. As stated in paragraph 7 of the Declaration of Michael Hagen, Ph.D, under 37 CFR §1.132 which accompanied the above referenced response, Dr. Hagen declared that one skilled in the field of Immunology would immediately recognize that a cytokine (GM-CSF) and a complex lipid (MPL) are not "art-recognized equivalents" compositions. Also, as stated in paragraph 7 of the Declaration of Michael Hagen, Ph.D, under 37 CFR §1.132, "Adjuvants and cytokines have inherently different mechanisms of action and, in my opinion, would not be considered as equivalents. An adjuvant works through the stimulation of a general immune response and can activate one or many different cytokines or chemokines during its course of action. Every cytokine or chemokine individually stimulates different pathways within the immune system. All of these pathways are different and every response by the immune system is different based on the adjuvant(s) used and the antigen administered with it. Cytokines, when administered to a subject, stimulate only one pathway. During the combination of an adjuvant and a cytokine, because of the different pathways involved, the immune response is unpredictable regardless of the individual mechanisms of action of the adjuvant and the cytokine. The other variable is the antigen itself. The administration of different antigens will yield a different immune response based on the individual properties of that particular antigen. The immune response generated from the combination of an antigen and an adjuvant and/or a cytokine is, again, unpredictable. There is no way in advance of knowing what will work until the appropriate experiments are completed." On page 5 of the Office Action dated December 4, 2008, the Examiner, without any basis, dismisses Dr. Hagen's declaration and found the declaration not persuasive.

Applicant maintains that complex lipid adjuvants and cytokines are different classes of compositions and are ***not*** art-recognized equivalents. It is respectfully submitted that the Examiner has continued to inappropriately equate the broad concepts of immune modulation and adjuvants to assert that all adjuvants and cytokines are art-recognized equivalents. Based on the fact that the Applicant's claimed invention is ***not*** the mixing of two equivalents, the Applicant respectfully submits that the Examiner's reliance on MPEP §2144.06 and *In re Kerkhoven* is therefore improper.

Applicants have previously noted that Boon et al. (WO 98/57659, hereafter "Boon") states that GM-CSF added to a combination of MPL and QS21 was "unable to enhance the effect of the QS21/MPL adjuvant". Boon is concerned with identifying the cytokine that would best augment the already known adjuvant combination of MPL and the saponin QS-21. Boon teaches that GM-CSF does not enhance the effect of an adjuvant formulation that comprises MPL adjuvant. The skilled artisan upon reading Boon would have been compelled to avoid addition of GM-CSF with MPL.

The Examiner continues to argue that the adjuvant formulation of Boon comprises more ingredients than those being claimed and rendered obvious by the cited art. The Examiner has also noted in the Office action dated March 19, 2008 on the bottom of page 12 that "the teaching of this reference has been noted, however any allegation of Boon et al. as a teaching away from

the claimed invention is moot for the rejection is not made over Boon". Applicant maintains that the MPL, QS-21 and GM-CSF combination of Boon argues firmly against the Examiner's continued insistence that the combination of **any** adjuvants, cytokines or a mix of adjuvants, cytokines and peptides, as in the Applicant's invention, should therefore work in combination. The Examiner asserts that all of these compositions are equivalents and that any combination should work to enhance an immune response to an antigen. Applicant maintains that if, as the Examiner states, that all of these compositions are indeed equivalents and would be obvious to combine to form a third composition used for the same purpose, then Boon's addition of GM-CSF to a MPL/QS21 combination should have enhanced the immune response. GM-CSF did not enhance the response. The Examiner has continued to underscore Applicant's argument that not all combinations will work in combination to enhance the immune response to an antigen.

Additionally, Applicant maintains that the Examiner's continued assertion that a response of a combination of an adjuvant and a cytokine is predictable is invalid. On the bottom of page 9 of the office action dated March 19, 2008, the Examiner insisted that it would be obvious to combine prior art elements to yield "predictable results". Applicant maintains that there is nothing predictable about the combination of Applicant's claimed invention. In the response dated September 19, 2008, Applicant submitted Mishkin et al. (US patent 6,488,936, hereafter known as "Mishkin") for additional argument against the notion that a composition comprising any adjuvant (alum) with any antigen with or without an immunomodulator (IL-12) will obviously produce an enhanced immune response. Data shown in Mishkin clearly showed examples of adjuvant, antigen and cytokine combinations that do not enhance an immune response in combination. Please see pages 19-20 of Applicant's response dated September 19, 2008. The data in this reference clearly shows that the immune response against the antigen in combination with a cytokine and an adjuvant was ineffective, therefore demonstrating that there is nothing predictable about the function of individual components when combined. The Examiner's argument that any combination of adjuvant and cytokine would synergistically increase an immune response to an antigen is negated by the data in Mishkin. In the Office Action dated December 4, 2008, the Examiner failed to comment on the arguments put forth by Applicant regarding Mishkin.

In contrast, Applicant has pointed to the data in the present application. Applicant maintains that the unique combination of MPL and GMCSF produces an enhanced effect on the immune response that is synergistic, not merely additive, as stated on page 20 of the present specification. For example, Applicant pointed to the data exemplified on page 46 of the present specification. The table shows each of the endpoint titers of IgG at weeks 4, 6 and 8. For example at the week 4 endpoint titers, 5 µg of antigen alone was administered to mice, which yielded less than a 100 IgG titer. The results were the same when GM-CSF and MPL-SE were administered alone with the antigen. In contrast, when MPL-SE, GM-CSF and the antigen were administered together the resulting titer was measured at 14, 824, which is seventy-four times higher than any additive effect. The same results are seen at week 6 and week 8. In fact, this synergistic response can be seen throughout the present specification in the Examples section. If the Examiner was correct in the statement that all combinations of adjuvants and cytokines would work to enhance an immune response, Applicant wishes to contrast the data presented in the present specification and compare this to the data in Table 1a of Exhibit A. The data clearly refutes the Examiner's contention that all cytokines, adjuvants and combinations thereof are predictable in their actions during combination.

As noted above he Examiner has further cited Bartlett to reject the claims that are limited to an HIV peptide. Applicant maintains that Bartlett merely evaluates the immunogenicity of polyvalent HIV envelope synthetic peptide immunogen in the presence of one adjuvant (incomplete Freund's adjuvant). The peptide taught in Bartlett, C4-V3, has the same amino acid sequence set forth in Applicant's SEQ ID NO:2. The combination of Ulrich and Disis, as already stated, does not render the claimed invention obvious and adding Bartlett's observations on a particular peptide does not change this result. There is nothing in the cited reference to suggest to the skilled artisan that the combination of MPL and GM-CSF would have been obvious alone with or without the addition the particular peptide taught in Bartlett.

Applicant maintains that there would have been no way to predict the synergistic effect of Applicant's claimed invention. There could have been no reasonable expectation of success previous to actual experimentation. In MPEP §2141 "Examination Guidelines for Determining

Obviousness Under 35 USC §103(a)", it states that the Supreme Court reaffirmed principles based on its precedent that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" KSR International Corporation v. Teleflex In. (KSR), 550 U.S. __, 83 USPQ2d 1395 (2007). Again, in MPEP §2143 "Examples of Basic Requirements of a Prima Facie Case of Obviousness" one of the "Exemplary Rationales" that may support a conclusion of obviousness includes combining prior art elements to yield ***predictable*** results. As stated throughout this brief as well as in the previously submitted Declaration, Applicant maintains that the Examiner has not sufficiently explained ***how*** or ***why*** Applicant's claimed invention is predictable.

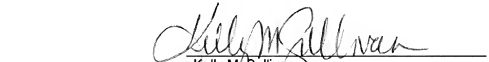
In summary, the Applicant maintains that the Examiner has continued to improperly apply *In re Kerkhoven* and MPEP §2144.06 by taking the broad terms "adjuvant" and "cytokine" and concluding that these two different elements of Applicant's claimed invention are art-recognized equivalents when clearly they are not, as argued as well as supported by the previously submitted Declaration. According to MPEP §716.01 "Generally Applicable Criteria" regarding Declarations under 37 CFR § 1.132, the Examiner is under the obligation to fully consider the Declaration submitted and sufficiently comment upon it's contents consistent with the guidelines provided under MPEP §1302.14.

Additionally, the Applicant further maintains that the Examiner has failed to establish a prima facie case of obviousness by failing to meet the standard of the KSR decision. The Examiner has failed to articulate why someone skilled in the art would have ***predicted*** the utility of the combination of elements in Applicant's claimed invention. In light of the arguments presented herein as well as the refuting exhibits showing lack of predictability of adjuvant and cytokine combinations and, in particular, the Declaration under 37 CFR 1.132, Applicant respectfully maintains that the rejection under 103(a) is improper.

Conclusion

According to the foregoing, it is respectfully requested that the panel find that all existing claims are in condition for allowance and that the application should pass to issue, or that there is allowable subject matter in the claims and prosecution on the merits should be reopened with an appropriate office communication.

Respectfully submitted,



Kelly M. Sullivan
Agent for Applicant(s)
Reg. No. 62,980
Telephone: (973) 660-5950

Wyeth
Patent Law Department
Five Giralda Farms
Madison, NJ 07940